Endogenous retroviruses and neighboring genes are coordinately repressed by LSD1/KDM1A.

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Public Summary:
Endogenous retroviruses (ERVs) constitute a substantial portion of mammalian genomes, and their retrotransposition activity helped to drive genetic variation, yet their expression is tightly regulated to prevent unchecked amplification. We generated a series of mouse mutants and embryonic stem (ES) cell lines carrying "deletable" and "rescuable" alleles of the lysine-specific demethylase LSD1/KDM1A. In the absence of KDM1A, the murine endogenous retrovirus MuERV-L/MERVL becomes overexpressed and embryonic development arrests at gastrulation. A number of cellular genes normally restricted to the zygotic genome activation (ZGA) period also become up-regulated in Kdm1a mutants. Strikingly, many of these cellular genes are flanked by MERVL sequences or have cryptic LTRs as promoters that are targets of KDM1A repression. Using genome-wide epigenetic profiling of Kdm1a mutant ES cells, we demonstrate that this subset of ZGA genes and MERVL elements displays increased methylation of histone H3K4, increased acetylation of H3K27, and decreased methylation of H3K9. As a consequence, Kdm1a mutant ES cells exhibit an unusual propensity to generate extraembryonic tissues. Our findings suggest that ancient retroviral insertions were used to co-opt regulatory sequences targeted by KDM1A for epigenetic silencing of cell fate genes during early mammalian embryonic development.

Scientific Abstract:
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